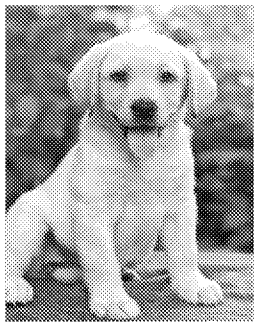
Seresto and EPA's Regulation of Pet Products



2021

Briefing for the OPP-IO

Melanie Biscoe, Jackie Herrick, Aaron Niman

Jackie

Purpose

- The purpose of this briefing is to:
  - Present OPP's regulation of pet products.
  - Provide an update on efforts to broadly address pet risk in OPP.
  - Discuss proposals to address incidents reported on the collar Seresto.

Jackie

U.S. Pet Product Regulation

- EPA regulates products applied directly to pets such as spot-ons, collars, shampoos, sprays, dips.
- In addition to typical data requirements, these products are supported by efficacy studies and a companion animal safety study.
  - The guideline for the companion animal safety study has not been updated in ~20 years and these studies are usually negative for adverse effects.
  - Small sample sizes and use of known hardy breeds detract from usefulness of these studies.
- Currently, both EPA and FDA have statutory responsibility in regulating products used on pets.
  - EPA regulates pet products applied to exterior of animals that are ***"not systemic."***

Jackie

FDA and EPA Regulation of Pet Products

- FDA regulates the majority of veterinary products in the U.S. and unlike EPA has extensive pre-market review and post-market surveillance programs under the Federal Food, Drug, and Cosmetic Act.
- Ex. 5 Deliberative Process (DP)

	Current EPA Requirements	Current FDA Requirements
Pre-market Animal Safety Study	Guideline No: 870.7200 Title: Companion Animal Safety Number of Animals: 6 per sex per dose Level of Concern: 5X Other: Harmonized with previous FDA/CVM Guidance #33	Guideline No: 185 (VICH GL43) Title: Target Animal Safety for Veterinary Pharmaceutical Products Number of Animals: 4 per sex per dose Level of Concern: 5X Other: International harmonization
Pre-market Clinical Trials	None	Guideline No: 85 (VICH GL9) Title: Good Clinical Practice Number of Animals ~200 (where 1/2 are positive control). Represents populations of actual pets rather than only test beagles. Informs labeling and contributes to the overall approval decision.
Post-market Surveillance	Aggregate summary reporting of summary numbers of adverse effects under FIFRA Section 6(a)(2). Generally only used to trigger a more detailed review.	FDA has dedicated post-marketing staff that monitor adverse reports to assure safety/effectiveness Findings may result in changes to product, label, insert, and communication with vets and the public.

Melanie

History of EPA Mitigation of Spot ons

- In 2009, due to an increase in reports of pet incidents involving spot-on pesticide products, OPP implemented the following measures for all spot-ons:
  - 2-year time-limited conditional registrations.
  - Label mitigation to clarify instructions for safe use and provide clear indicators to prevent misuse.
  - Limitation on CSFs to one formulation.
  - Enhanced quarterly incident reporting with corresponding sales data (such as exposure scenarios and associated clinical signs).
- In 2018 OPP and 5 companies concluded a pilot using uniform templates for enhanced reporting.
  - Efforts are currently underway to request all registrants to submit their reporting in this new form.
  - As an incentive to report in the new form, EPA has agreed to remove the 2-year time-limitation registration and convert the reporting requirement from quarterly to annual.

Jackie

Ex. 5 Deliberative Process (DP)

Pet Incidents Issue

- OPP currently has no standardized process for evaluating any pet incidents, nor a defined precedent for when pet incidents trigger further review or potential action.
- Current 6a2 incident reporting information and Section 7 production data information are not sufficient to allow EPA to analyze the frequency of incidents compared to product sales.
  - Incidents are aggregated - no narrative or specific information is required in typical reporting requirements.
  - Unlike FDA's Adverse Event Reporting System (FAERS), EPA does not have a centralized reporting system for collection of enhanced data. This results in reporting inconsistencies that make it difficult to compare products across companies.

Melanie
In Registration Review, PIDs and IDs discuss ongoing efforts to review incidents, but to date we have not published pet incident data in our decision documents.

Pet Incidents Issue

- In Registration Review, potential human health risks of concern have been identified from use on pets for several chemicals (*e.g.*, fipronil, amitraz) currently being evaluated. Regulatory actions based on pet incidents should not drive consumers toward products with potential human health risks of concern.
- In March 2019 the OPP OD was briefed on team recommendations for cross-product review of pet incident information, **Ex. 5 Deliberative Process (DP)**

Ex. 5 Deliberative Process (DP)

Melanie

Seresto Background

- The Seresto pet collar, containing imidacloprid and flumethrin, was registered in 2012 by Bayer. It is now owned by Elanco.
- The collar can be marketed for all sizes of cats and dogs for treatment against fleas, ticks, and lice.
- The collar is used on Arizona tribal lands and has successfully reduced the number of Rocky Mountain Spotted Fever infections in local tribal communities.
- We have received more than 75,000 incidents, including 1,698 pet deaths on the collar since it was registered in 2012.

Jackie

Seresto Background

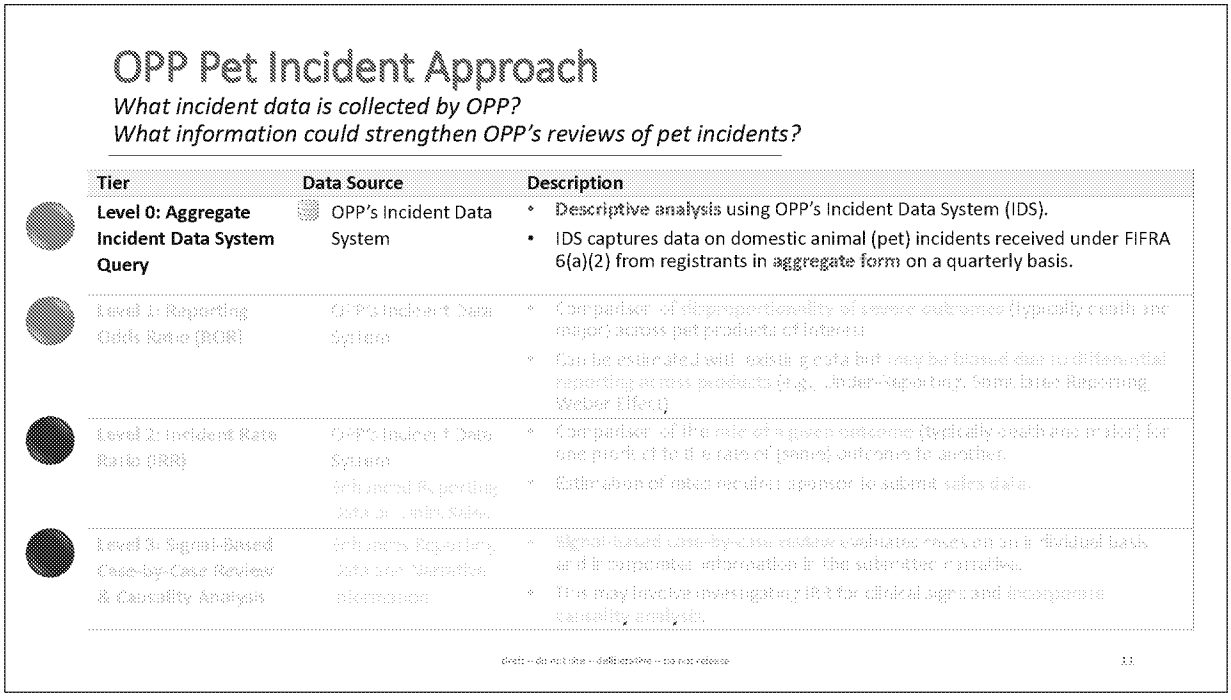
- Seresto is registered in the EU with label mitigation that identifies possible side effects and directs the user to remove the collar in those instances.
- In 2016, PMRA did not register Seresto **Ex. 5 Deliberative Process (DP)**

Ex. 5 Deliberative Process (DP)

- The Registration Review Interim Decision for flumethrin was completed in March 2020
  - Noted the increase in pet incidents, but no label changes were required for pet safety due to limited pet incident analysis available.
- The Registration Review Interim Decision for imidacloprid is scheduled to be completed later this year.

Melanie

Jackie
At some point after the conclusion of PMRA's review, Bayer refused to give permission for the continued collaboration between the two agencies in review their product.


OPP Pet Incident Approach
What incident data is collected by OPP?
What information could strengthen OPP's reviews of pet incidents?
Tier
Data Source
Description
Level 0: Aggregate Incident Data System Query
OPP's Incident Data System
Descriptive analysis using OPP's Incident Data System (IDS).
IDS captures data on domestic animal (pet) incidents received under FIFRA 6(a)(2) from registrants in aggregate form on a quarterly basis.
Level 1: Reporting Odds Ratio (ROR)
OPP's Incident Data System
Comparison of disproportionality of severe outcomes (typically death) are major) across pet products of interest.
Can be estimated with existing data but may be biased due to differential reporting across products (e.g., Under-Reporting, Some Time Reporting, Weber Effect).
Level 2: Incident Rate Ratio (IRR)
OPP's Incident Data System
Supplemental Reporting Data or Sales Data
Comparison of the rate of a given outcome (typically death are major) for one product to the rate of [same] outcome for another.
Estimation of most recent quarter to submit sales data.
Level 3: Signal-Based Case-by-Case Review & Causality Analysis
Registrants Reporting Data and Narrative Information
Signal-based case-by-case review evaluates events on a individual basis and incorporates information in the submitted narrative.
This may involve investigating PET for clinical signs and incorporate causality analysis.
Draft – do not cite – deliberative – do not release
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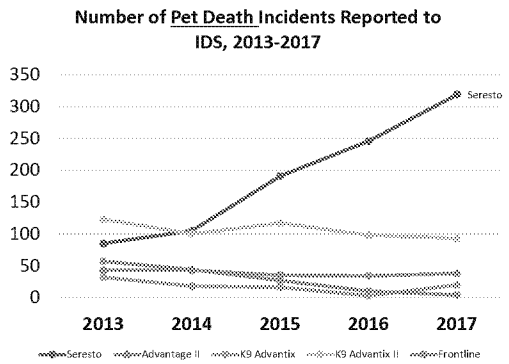
Aaron

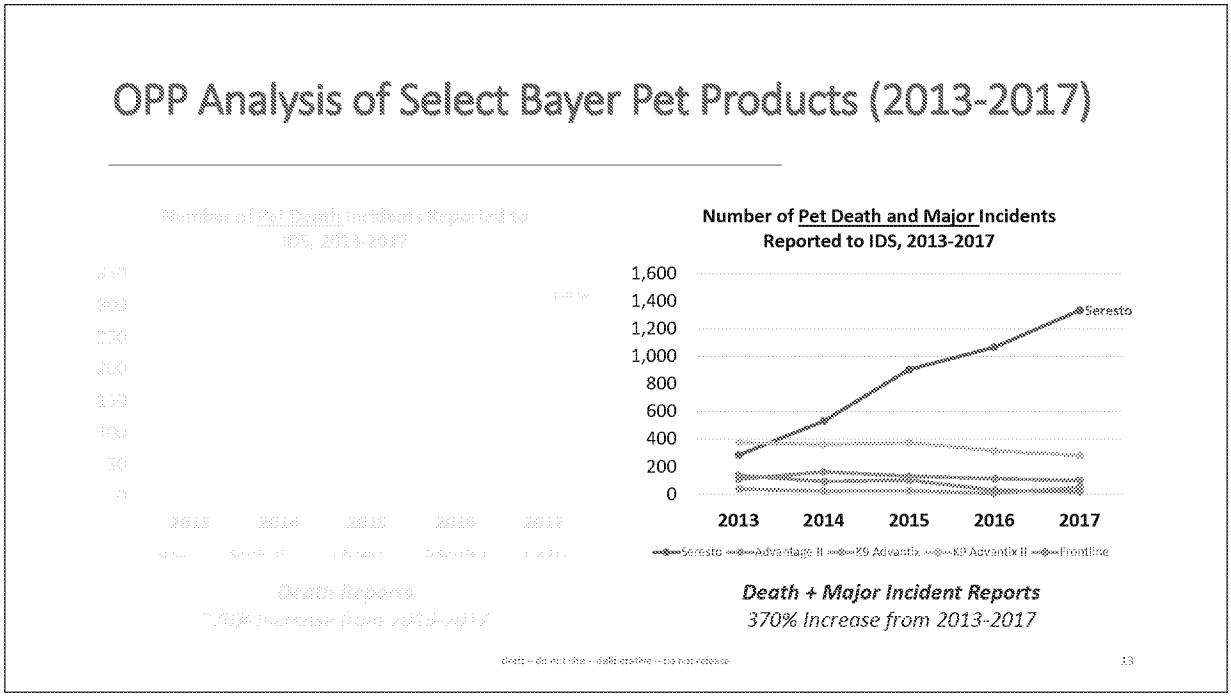
OPP Analysis of Select Bayer Pet Products (2013-2017)



Death Reports

270% increase from 2013-2017

Aaron
Incident data alone show there are more incidents for seresto when compared to other bayer products. Shows why people are concerned – this is the only information we typically see that there may be an issue70% increase



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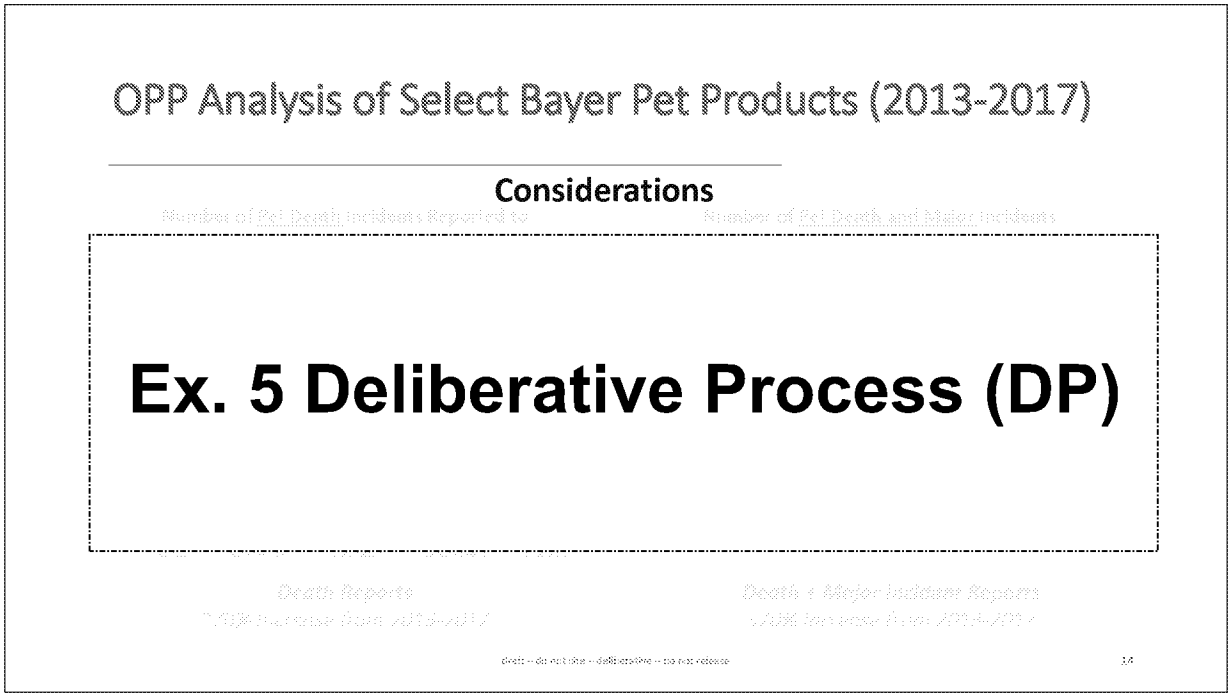

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Status of OPP Review of Seresto Pet Incidents
Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)
draft -- do not cite -- deliberative -- do not release
35

Aaron

Status of OPP Review of Seresto Pet Incidents

- **Bayer Presentation to EPA (July 2019 Meeting)**
  - Company representatives presented analysis of incidents trends that accounted for Seresto market share. Company suggested:
    - Incident reporting has decreased as U.S. market share has increased.
    - Seresto incidents trend is normalizing and is now on par with the safety profile of K9 Advantix.
  - While Bayer shared some summary information during the meeting, the company has not formally submitted the underlying data and supporting documentation. As such, OPP has been unable to replicate their findings and examine further.

Aaron

Status of OPP Review of Seresto Pet Incidents

- **Data Limitations and Needs**
  - OPP can continue to perform descriptive analysis of trends
  - However, sales data and narrative information needed to fully assess incident trends and link use with severe outcomes and death.
    - Updated comparison of incident rates relative to product market share
    - Narrative review of clinical symptoms and causality assessment
  - Information requested in Excel-reporting template (2016) for spot-on products pilot would allow comparative product analysis of Seresto and related pet products.

Aaron

Current Seresto Issue

- We continue to receive reports of pet incidents.
  - In 2019, 384 pet deaths were recorded.
  - Neurological signs and seizures anecdotally appear to be related to the collar's use
- In March 2021, USA Today published an article after receiving an aggregate incident report via FOIA.
  - As of 3/17 there have been 2 Congressional inquiries on the incidents since the article published.
  - 75,000 incidents, 1698 pet deaths, and nearly 1000 human incidents over 8 years.
  - Preliminary analysis of 2020 data adds another 11,000 total incidents.
- **We need sales data and additional incident details to give context to the incident numbers.**

Jackie
*Elanco stated they did not think they could submit incident data electronically so were holding off on paper submissions until we returned to the office.

EPA's Regulatory Options under FIFRA

1. Suspension under Section 6

- A Notice of Intent to Cancel (NOIC) must be issued at the same time as a suspension order unless EPA determines an emergency exists.
  - In the case of emergency the NOIC must be issued no later than 90 days after the emergency suspension order.
- To issue an NOIC, EPA must determine that the product as registered does not appear to meet the FIFRA standard.
- Both a suspension order and NOIC afford the registrant the right to request a hearing.

2. Enforcement under Section 13a

- A Stop Sale, Use, or Removal Order (SSURO) when EPA has reason to believe on the basis of inspections or tests that the product is in violation of FIFRA.
- EPA has no authority to require product recall but registrants may volunteer to recall products.

Jackie
Potential label mitigation: Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

Data considerations:
When do we anticipate to receive the data?
Who would review the data? How would OPP evaluate and implement?
We do not currently have a standard that details how many incidents are needed to determine this product is unsafe.

As of 2018, 178 of the 417 registered pet products (43%) are from spot-ons which are already required to submit enhanced reporting data, while an additional 40 products (10%) are collars. The remaining pet products (47%) are dips, sprays, otic applications, tags, powders, shampoos, and wipes. However, over 90% of all pet incidents reported are from collar and spot-on applications.

Recommended Next Steps

1. Ex. 5 Deliberative Process (DP)

2. **Regulatory Options for Seresto**
   a. **Get Seresto sales data and detailed data on neurological symptoms found in incidents, then analyze in conjunction with 6a2 incident data. OPP could obtain Seresto data by:**
      i. Requesting that Elanco provide it voluntarily
      ii. Issuing 6a2 letter
      iii. Issuing a Data Call-In (DCI) through registration review (OMB review is needed for this option)
   b. **Ex. 5 Deliberative Process (DP)**

For all Seresto-specific options, Elanco likely will push back that EPA is unfairly targeting its product

Jackie
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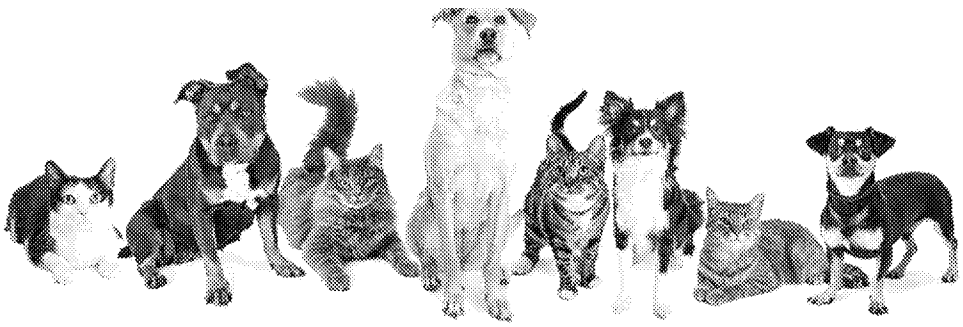

Thank You! Questions?

EU Label Language

Source: Product leaflet from the EU Head of Medicines Agency
https://mri.cts-mrp.eu/Human/Downloads/DE_V_0143_004_FinalPL.pdf

6. ADVERSE REACTIONS

In rare cases behavioural disorders that may include hiding, vocalization, hyperactivity, excessive licking and/or grooming or scratching at the application site may be observed in animals that are not used to wearing collars on the first few days after fitting. Aggression after collar application was reported in very rare cases. Ensure that the collar is fitted correctly.
Application site reactions such as pruritus, erythema and hair loss may occur. These have been reported as rare and usually resolve within 1 to 2 weeks. In single cases, a temporary collar removal may be recommended until the symptoms have disappeared.
In very rare cases, application site reactions such as dermatitis, inflammation, eczema, lesions or haemorrhage may occur and in these instances, collar removal is recommended.
In rare cases neurological symptoms as ataxia, convulsions and tremor may occur. In these cases collar removal is recommended.
Also in rare cases in dogs, slight and transient reactions as depression, change of food intake, salivation, vomiting and diarrhea might occur initially.
The frequency of adverse reactions is defined using the following convention:
-very common (more than 1 in 10 animals treated displaying adverse reaction(s))
-common (more than 1 but less than 10 animals in 100 animals treated)
-uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
-rare (more than 1 but less than 10 animals in 10,000 animals treated)
-very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

If you notice any side effects, even those not already listed in the package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Melanie

Congressional Inquiries

1. Raja Krishnamoorthi – Chairman – Subcommitte on Economic and Consumer Policy – due 3/30/21

- A description of IDS.
- A list of all pet products in IDS with pet death/injury or human death/injury.
- Policies and procedures regarding various aspects of IDS.

2. Bernard Sanders, VT

- Requests response to constituent letter.
  - Letter demands EPA to immediately issue a stop sale.